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THE DIFFERENTIATION
OF THE CONTINUED AND REMITTENT FEVERS
OF THE TROPICS BY THE BLOOD CHANGES

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BY

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The great advances made during the last few years in the microscopical methods of diagnosis of malaria and typhoid fever respectively have placed in our hands the power to differentiate, with far greater accuracy than was previously the case, these, the most frequently met with and most important of tropical fevers. Further, by combining these two, we are enabled to investigate, with much greater hope of obtaining at least approximately correct results, the very difficult and all-important question as to whether there are any as yet undifferentiated forms remaining to be specially specified and described. The large number of Calcutta hospitals in untravelling field for such an inquiry, and, owing to the

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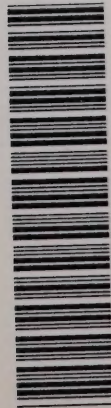
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The great advances made during the last few years in the microscopical methods of diagnosis of malaria and typhoid fever respectively have placed in our hands the power to differentiate, with far greater accuracy than was previously the case, these, the most frequently met with and most important of tropical fevers. Further, by enabling these two to be separated out, we are enabled to investigate, with much greater hope of obtaining at least approximately correct results, the very difficult and all-important question as to whether there are any as yet undifferentiated fevers remaining to be carefully examined and described. The large hospitals of Calcutta furnish an unrivalled field for such an inquiry, and, thanks to the

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great kindness of the medical staffs of these institutions (all of whom are officers of the Indian Medical Service, to whom I desire to express my great obligation), I have been able during the last year and a half to examine the blood and carry out the serum tests in about two hundred continued and remittent fevers of all kinds, in both the Presidency General Hospital, which admits European patients only, and in the Medical College Hospital, where the majority of the patients are natives of India. The cases have been taken consecutively, as far as possible, every case being examined when time permitted. Further, I have in my possession clinical notes of the cases and four-hour temperature charts, which have been carefully analysed in order to see how far a study of series of different forms of continued and remittent fevers, as proved by the blood and serum examinations, will enable any rules of value to be laid down for their clinical differentiation. The subject is too vast a one to be treated adequately within the limits of a single paper, but the principal conclusions which have been arrived at may be set forth, and the evidence on which they are based may be summarised.

The nomenclature and classification of tropical fevers adopted by various Indian writers are too varied to be referred to in detail, so it will be best to start with that which Crombie laid down in his address in the Medical Section of the Indian Medical Congress of 1894 (1), which may be taken as a valuable summary of what can be said on the subject of the differentiation of Indian fevers, by means of purely clinical methods, by an observant physician of great experience, mostly acquired in the very hospitals in which I have been recently working. In addition to malarial intermittent and remittent fevers, Dr. Crombie, in his presidential address in Medicine and Pathology at the First Indian Medical Congress in 1894, describes under the head of "Continued Fevers" three certain and two more doubtful forms, as follows:

1. *Simple continued fever*, lasting three to eight days,

and including three fourths of the fevers commonly returned under the head of "ague" in India.

2. *Typhoid fever*, extremely rarely found in natives.

3. "*Non-malarial remittent*," lasting three to six weeks, commonly fatal, and mostly seen in natives.

Doubtful fevers.—4. "*Calcutta fever*" or "*Bombay fever*," being an aggravated "simple continued fever," lasting fourteen, twenty-one, or twenty-eight days.

5. *Low fever*, the temperature varying from 99° to 101.5°, being very persistent, not affected by quinine, but often cured by a complete change.

No. 3 he regards as being the most important undifferentiated fever remaining to be thoroughly investigated and its organism identified. It was mainly in the hope of separating it, and perhaps other fevers, so as to be able to search for its cause, that the investigation now being described was undertaken. Nearly all the long-continued fevers occurring in the large Medical College Hospital have been examined in the pathological laboratory for a space of eighteen months; and at the same time nearly daily visits were made to the General Hospital at the other end of the town for the purpose of examining all similar cases there. In order to simplify matters as much as possible and to avoid repetition, it will be best to first describe my methods and results, and then to compare them with Dr. Crombie's clinical types.

METHODS OF RESEARCH. THE DIFFERENTIAL LEUCOCYTE COUNT.

In addition to the serum tests for typhoid and Malta fever, and the search for malarial parasites, a new method described by me a year ago (2) has proved of the greatest value in this inquiry—namely, the increase in the percentage of lymphocytes in typhoid, and of the large mononuclear white corpuscles in malarial fevers, by which means alone, in the great majority of cases, a correct diagnosis can be arrived at by the examination of stained

blood-films with an ordinary high-power lens. My earlier results have been amply confirmed by the much larger series of cases since examined, while Captain T. H. Delany, I.M.S. (3), has obtained precisely similar results in upwards of one hundred cases examined by him in the Medical College Hospital. The great advantage of this method lies in the fact that the result is in no way interfered with by the previous administration of quinine, as is the search for malarial parasites. As long ago as 1896 (4) I showed, from an examination of one hundred consecutive malarial fevers before the administration of quinine, that in only one third of them could the malarial parasite be found by means of a prolonged search of a single blood-film; and the absence of the parasite from the peripheral circulation in untreated cases has recently been emphasised by Stephens and Christophers (5). In a still larger proportion of cases which have been treated with quinine will negative results be obtained. Thus Maynard (6), working in the Calcutta General Hospital in 1895, found parasites in only 25·7 per cent. of seventy malarial fevers, nearly one half of which had previously taken quinine. As in my present series quinine had been nearly invariably given before I was able to examine the blood, the search for the parasites was negative in the great majority of the cases examined, and no conclusions can be drawn as to the proportion of malarious fevers in the series from the number in which parasites were found. This is also in entire accordance with Captain Delany's recent results (3), for in only 17 per cent. of undoubted malarial fevers examined by him were parasites found, on account of the previous exhibition of quinine, while in over 90 per cent. he was able to correctly diagnose them by the large mononuclear leucocyte increase. It is worthy of note that Captain Delany and myself frequently independently did counts on the same cases at different times, yet never arrived at a different diagnosis. The constancy with which a positive Widal reaction for typhoid has been accompanied by an absence of any large mononuclear

increase, while on the other hand a negative reaction together with a large mononuclear increase has been found in nearly all cases which were either obviously malarial clinically, or which were subsequently proved to be so by their reaction to the quinine test in this large series of cases, appears to me to be in itself conclusive as to the great diagnostic value of the leucocyte count. Stress is laid on this point at the outset, because much of any value in the differentiation and classification of tropical fevers this paper may possess depends on the correctness or otherwise of this new test in addition to the serum reaction. I have already described the method of counting which I have adopted, so need not repeat it here. Briefly, it may be said that blood-films were made by spreading out a small drop of blood on a slide by means of the gliding motion of a needle; they were fixed in alcohol, and stained by Romanowsky's method. Counts were made by working from edge to edge of the middle of the film. Mononuclears, which were as large as or larger than the average polynuclears, only were counted as large mononuclears. From 250 to 500 leucocytes were counted, the smaller number having been found to be quite reliable in most cases after some experience.

The importance of recording the temperature every four hours scarcely needs emphasising, and its value in differentiating between the continued type of many typhoids and the severer forms of malarial remittents will be dealt with later on.

TYPHOID FEVER IN EUROPEANS.

It will be well to deal with this, the best known continued fever of the tropics, first, so as to be able to have a standard with which others can be compared. During the last year an unusually large number of cases of typhoid fever have been admitted to the European General Hospital, as will be seen from a glance at the upper curve of Diagram I, so that out of 126 cases of all

kinds examined by me in this hospital during the past year and a half, no less than 50 were typhoid. The notes and blood examinations of these have been tabulated in shorthand, so a brief analysis of the most important points regarding them may be given.

Age-incidence.—This is shown in the following table:

Table of Age-incidence.

Years 5 . 5-10 . 11-15 . 16-20 . 21-25 . 26-30 . 31-40 . Over 40	Total.
Cases 2 . 3 . 11 . 18 . 7 . 6 . 1 . 2 . 50	

The percentages in each period can be obtained by doubling the figures given, and it will be seen at once that the age distribution of these cases is typically that of typhoid fever.

Table of Duration of Fever.

Days . 1-7 . 8-14 . 15-20 . 21-25 . 26-30 . 31-40 . Over 40	
Cases . 1 (died) . 2 . 8 . 19 . 7 . 6 . 7	

In the very great majority of these cases among Europeans accurate histories can be obtained, so the accompanying data with regard to the duration of the fever are fairly reliable, although doubtless two or three days at the beginning of some of the milder and shorter cases may have been overlooked by the patients or their relations. In only two cases did the fever last less than 15 days (omitting one case fatal on the 5th day), these being abortive cases which will be referred to again. In eight more cases the fever is recorded as having lasted less than 21 days, one of which proved fatal on the 17th day. Three of them lasted 18 days, one 19, and the other three 20 days. These were mostly mild cases in which an insidious onset may have been overlooked for a time. Of the above cases lasting less than three weeks, all but two were in patients under 21 years of age, typhoid being well known to be milder in young persons. Between the

ages of from 21 to 25 days, nineteen cases, or 38 per cent. of the whole, fall; while seven cases lasted from 26 to 30 days, six cases from 31 to 40 days, and the remaining seven upwards of 40 days, including four cases in which relapses occurred, the longest time having been 69 days. These figures are also characteristic of typhoid fever.

Clinical characters.—With the exception of a few mild cases, which did not show very marked symptoms of typhoid fever, but were diagnosed by the serum test, the series was as a whole typical of the disease, and most of them had either been diagnosed as typhoid or were suspected to be such before the blood examination was reported. In thirty-nine of them looseness of the bowels, with more or less characteristic stools, was noted at some period or other of the fever, while thirteen showed constipation. In four hemorrhage was noted, in one of which it was attributed to coincident dysentery. Characteristic spots were noted in sixteen cases, while in thirteen they were recorded as having been absent. During the hot and rainy season prickly heat is often so extensively present as to make a search for typhoid spots a difficult and uncertain proceeding, but for which they would probably have been found in a larger proportion of cases, for I find they are more frequently detected in the cold weather months, and they are undoubtedly of great diagnostic value in Europeans, even in the tropics. Abdominal symptoms are of the utmost diagnostic importance, as in only eight cases was the abdomen noted as normal, and that usually in an early stage of the disease; while in eight more there was no note on the subject, the clinical records having been scanty in some of the milder cases. In the remaining thirty-four, or 68 per cent., either distension, tympanites, or tenderness, or, most frequently, two or more of these symptoms together, were noted. The spleen was felt below the edge of the ribs in only twelve cases, and the liver in fifteen cases. The pulse was frequently noted to be dicrotic, and bronchial catarrh or congestion of the bases of the lungs also occurred fairly frequently. All

the above points taken together constitute a typical clinical picture of a series of typhoid fever cases, which will serve for comparison with other tropical continued and remittent fevers, and only the important question of the type of the fever curve remains to be considered under this heading.

The temperature curve.—The clinical differentiation between a continued and a "remittent" type of fever, although simple enough in well-marked cases, presents difficulties when it is desired to draw a hard and fast line between them. As, however, the separation of the continued type, so characteristic of most cases of typhoid, from the "remittent" type of severe malarial fevers is of the utmost practical importance, an attempt must be made to draw the line somewhere. Bearing in mind that the malarial remittents are caused by the malignant tertian parasites, we should expect a marked remission at least every other day in these cases; while any case in which the temperature varied through a range of only two degrees or less for slightly over forty-eight hours (to allow for some degree of "postponement" in malarial remittents running a favourable course) may be considered to be of a "continued" type. The practical value of this definition will appear presently, and we may now see how frequently this "continued" type occurs in typhoid fever, and how early it is present in a characteristic degree. An examination of the four-hour temperature charts of my fifty typhoid cases from this point of view gave the following results. During the first week of the disease there were admitted twenty-nine cases, of which twenty were admitted on or before the 5th day, and eleven on or before the 4th day, leaving 3 and 4 days respectively of the first week for observation in hospital, yet eight of them showed the "continued" type within that time. During the second week twenty-one more cases showed it, and two others during the third week, and three at later dates. Thus thirty-four out of the fifty cases presented this feature at some time or other in the course of the

disease, the great majority of which showed it well before the end of the second week. On the other hand, in fourteen cases the remissions of the fever were more marked, while in two cases in young children the curve was intermittent throughout. The persistence of a high degree of fever is also an important point to note, for in typhoid cases it is common for the temperature to remain persistently above 102° for days together; while we shall see presently this and the "continued" type of fever very rarely occur in acute malarial remittent fevers.

Death-rate.—This was 6 per cent., only three cases having died out of the fifty. This points to the very high mortality of 25 per cent. and upwards returned frequently in the British Army in the tropics being due to mild cases being often overlooked.

The serum reaction.—The serum reaction was tested in each case with one-day broth cultures in dilutions of 1 in 20, 1 in 40, and 1 in 100 under the microscope, with a time limit of one hour, and only recorded as positive when all active motion of the bacilli had ceased within that time as well as good clumps had formed. Many of the cases were tested more than once, and not infrequently during the later stages a reaction was obtained in a higher degree than in an earlier test, which could only be due to the actual presence of typhoid fever and not due to any previous attack.

Table of Serum Reactions.

	- 1 in 20.	+ 1 in 20.	+ 1 in 40.	+ 1 in 100.	Total.
First week	1	2	2	—	7
Second week	7	2	3	10	22
Third week	6	1	6	7	20
Later	5	—	3	10	18
Total.	19	5	14	27	67

The above table shows the results of the serum reactions in each week of the disease, and the degree of reaction obtained. The nineteen negative reactions include seven cases

in which no reaction was obtained, although six of them were twice tested, the day of the last test having been from the 19th to the 30th days. In one instance, however, the blood was not examined until the temperature had been normal for eight days, in which time a previously present agglutinating power may have disappeared. (Horton Smith). In the other cases a positive reaction was obtained at a later date. Similarly some of the cases, which at the first test gave only reactions in the lower dilutions, reacted in 1 in 100 at a later date. Reactions were obtained at some period of the disease in 43 cases, or 86 per cent. The cases which did not react have been diagnosed as enteric on account of the clinical evidence of the presence of this disease being very strong, and being confirmed by the leucocyte count, to be described immediately. It will be noted that in the great majority of the cases reactions in dilutions of 1 in 40 and upwards were obtained, which, in my experience, are quite conclusive of typhoid fever, although I have twice met with a reaction in a dilution of 1 in 40 one and two years respectively after a previous attack, but never up to 1 in 100 except during concurrent typhoid fever. The occasional absence of a reaction in typhoid cases is an experience common to various observers, but I have not had any opportunity of making bacteriological examinations for the presence of the group of bacilli which have been found in the so-called paratyphoids in America recently, so cannot say if they should be classed as such or not.

The lymphocyte increase in typhoid.—I have elsewhere (2) drawn attention to the value of a marked increase of the percentage of lymphocytes without any noteworthy increase of the large mononuclear white corpuscles, in differentiating typhoid from malarial remittent fevers; and subsequent experience of a large number of cases has amply confirmed, and in some respects extended, my earlier results. My former paper on this subject was largely based on cases of fever in natives, who very frequently do not come to hospital until far on in the disease, so that

the great majority of the cases were not examined until the third or fourth week, when a well-marked lymphocyte increase was nearly uniformly met with in uncomplicated cases. In the present series in Europeans many were examined in the earlier stages, so that they furnish a better evidence as to the diagnostic value of this change in the blood. In the following table the number of examinations in each week of the disease, in which varying degrees of lymphocyte increase were found, is shown in a convenient form for studying the degree and frequency of the change.

Table showing Lymphocyte Increase in Typhoid.

First week	No increase = 26.				Increased = 46.					Total
Number of lymphocytes	— 20	20-25	25-30	30-35	35-40	40-50	50	50	50	71.
First week	—	—	2	1	1	1	—	—	5	5
Second week	3	—	7	4	5	4	1	—	24	24
Third week	4	1	1	2	3	5	4	—	20	20
Later	4	3	1	3	2	7	3	—	23	23
Totals	11	4	11	10	11	17	8	—	72	72

Of the fifty cases there was no increase in twelve, and an increase in thirty-eight cases, or 72 per cent.

From the above table it appears that the lymphocytes were increased above the normal limit of 30 per cent. in about three quarters of the cases, and this change may even be found in the first week, and in the majority of the cases in the second week, and in almost three quarters of them during the third week of the disease, when it frequently reaches a high degree. Its value, however, is even greater than these figures denote, for as a rule the cases in which it is absent are of a severe type, which can be recognised as probably typhoid fever at a glance, while in the mildest cases it is usually particularly well marked; that is just where it is most wanted. The absence of the lymphocyte increase late in the disease is a bad prognostic sign, while when a severe case in which it has been absent begins to improve, it rapidly appears, so

that there seems to be some relationship between the establishment of immunity and the lymphocyte increase. When in a case of continued fever the lymphocytes are increased, and especially if over 35 per cent. are found, and at the same time there is no marked increase of the large mononuclears (which is so characteristic of malaria), then it is exceedingly likely to be a case of typhoid fever. In cases of malarial remittent fever a similar count may rarely be obtained at the height of the daily rise of temperature; but in these cases the total number of leucocytes present will be very greatly reduced, usually to about 1000 per c.mm.—a condition which I have only seen in malarial and never in typhoid cases. It is important, then, to note the percentage of large mononuclears met with in the series of typhoid cases, so that they may be compared with that of the malarial series to be dealt with presently. The following table shows the results obtained.

Table of Large Mononuclear White Corpuscles in Typhoid.

	Normal.				In excess.		Total.
	—4	4-8	8-10	11-15	+ 15		
Percentages . . .	—4	4-8	8-10	11-15	+ 15		
Total examinations . .	37	24	4	4	3	72	
First and second weeks . .	—	—	1	1	1		
Third week . . .	—	—	—	—	—		
Later . . .	—	—	—	3	2		

From this table we find that in only eleven out of seventy-two examinations were the large mononuclears above the normal 8 per cent., and in only three was the increase found during the first three weeks of the fever, when the diagnosis might possibly have been in doubt. In one of these malarial parasites were found in the blood, the large mononuclears having numbered 18 per cent.; and in another, in which 15.6 per cent. were found, typhoid had supervened on a malarial fever; and in the remaining one there were reasons for believing that the typhoid was also complicated by malaria. The highest number of large mononuclears met with in a typhoid patient was

18 per cent., and malarial parasites were also found in the blood at the same time as a Widal reaction was obtained in a dilution of 1 in 100 (Case 6). In the remaining instances in which over 10 per cent. were found the fever had reached from the thirty-fourth to the seventy-ninth day, and normal numbers of large mononuclears had been found in the earlier stages. It is clear, then, that the occasional high percentage of these corpuscles in the blood of typhoid patients in the earlier stages of the disease usually denotes coincident occurrence of malarial infection, which requires appropriate treatment; while in the later stages there may be some increase after the end of the third week in prolonged cases of pure typhoid, but this can scarcely mislead at such a late period of the disease. A similar late large mononuclear increase has been recorded by Winter in Dublin (10). Asweshall see immediately, a marked large mononuclear increase is so characteristic of malarial remittent fevers that its absence should lead to a suspicion of typhoid as against malaria, and that, too, even in the absence of a marked increase of the lymphocytes. I have several times correctly diagnosed cases of typhoid in an early stage by this point, leucocytosis of pneumonia or cerebro-spinal fever, etc., being also absent.

TYPHOID IN NATIVES OF INDIA.

The frequency or otherwise of typhoid fever in natives of India was a perennial source of controversy in the pre-Widal days. As the subject is of great importance in relationship to the so-called "non-malarial remittent" fever of Crombie, it must be briefly referred to here, reference being made to a paper in which I dealt more fully with the subject a year ago for further details (7). Dr. Crombie used to hold that typhoid very rarely occurs in natives, and supported his conclusion by the statement that only three cases were returned as such in the large Medical College Hospital in the ten years from 1880 to 1889. By means of the serum test I found twice that number in

the wards of the same hospital at one time, and eleven cases in five months. That number has in the course of eighteen months been increased to twenty-six, together with others in different hospitals and institutions in Calcutta; while reactions in high dilutions have also been obtained with the blood of native fever patients sent me from various parts of Bengal. Lamb has also obtained similar results in Bombay. Clinically they do not differ essentially from the same disease in Europeans, only they tend to be more severe and fatal on account of the late stage of the disease in which they are commonly admitted; while bronchial affections are more common, and diarrhoea less so than in Europeans, the stools being less typical, probably on account of the largely vegetarian diet of the great majority of the patients. The disease is also somewhat more common among children in natives, no doubt on account of their greater exposure to insanitary conditions. More important are the duration and type of the fever for comparison with those of other fevers. Out of twenty-one cases of typhoid in natives, with confirmation by Widal's test in the Medical College Hospital, of which I have full notes, five died before the end of the third week. Of the remainder, all but one suffered from fever for three weeks or more, the exception having only given a reaction in a dilution of 1 in 20, and clinically also the diagnosis of typhoid was not quite beyond suspicion. Nine cases lost their fever between the twenty-first and the twenty-fifth day, and the other six at later dates. These results agree closely with those recorded above in typhoid in Europeans, and lend no support to the view that the disease is commonly abortive and of short duration in natives, although it may very occasionally be so. With regard to the type of the disease, in just half of the cases the "continued" type, as defined above, was observed; that is a somewhat smaller proportion than in Europeans, possibly due to the greater frequency of complication with a malarial element in the case of natives. In the other cases the fever was of a remittent type,

although usually less markedly so than in true malarial remittents. Abdominal symptoms, such as distension, tympanites, or pain, were nearly always met with at some period of the disease—a most important clinical diagnostic feature. With regard to the serum test, reactions in dilutions of 1 in 20 only were obtained in two; in 1 in 40 in six more; and in 1 in 100 in eighteen cases,—a result closely comparable with those in Europeans. Similarly with the leucocyte count: in two thirds of thirty examinations a lymphocyte increase to above 30 per cent. was found, in all but four of which over 35 per cent. were present. On the other hand, in twenty-seven examinations the large mononuclears were not over the normal limit of 8 per cent., and in the remaining three cases they were under 9 per cent., which, we shall see presently, clearly differentiates them from malarial remittent fevers.

The above brief summary is sufficient to prove that typhoid fever is a common continued fever of natives of India, and that it differs in no noteworthy respect from the same disease in Europeans in this country.

MALARIAL REMITTENT FEVERS.

We next have to deal with the great class of malarial remittent fevers, whose differentiation from typhoid in their earlier stages is, in many instances, one of the most difficult problems in tropical medicine. In the first place we must define the term "remittent," and draw some line between it and intermittent cases; for these terms are often very loosely used, different meanings being attached to them by various observers. For instance, in many cases of malignant tertian malarial fever the temperature remains high for some thirty-six hours, and then falls to about normal for a few hours before the same cycle is repeated. This is essentially an intermittent type, and the term remittent should be reserved for those cases in which the temperature remains well above the normal line for some days. In an analysis of the General Hospital records to ascertain

the seasonal prevalence of the different forms of fever, therefore, I adopted the plan of classing cases under the head of "remittent fever" only when the temperature did not fall below 100° F. for two or more clear days; and the following data are also based on a series of cases complying with this definition. I find in my tables twenty-nine acute malarial remittents in the European General Hospital, which both the clinical course and the result of the exhibition of quinine clearly proved to be malarial. Further, they were all examined by the serum test for both typhoid and Malta fever, with negative results in all but one man, who had suffered from a severe attack of typhoid fever in South Africa two years before, and whose blood gave a reaction in a dilution of 1 in 40. All these cases had been liberally dosed with quinine before I had an opportunity of examining their blood, so that the fact that in only a small proportion of them were malarial parasites found in no way negatives their malarial nature. Moreover, as we shall see presently, nearly all of them showed the typical large mononuclear increase of malaria, which fortunately is not masked by quinine, and hence has a peculiar diagnostic value in such a series as this. By analysing them in a similar manner to the former series of typhoid cases, we shall be able to get a clear idea of the diagnostic value in the two fevers of the blood changes; and if these are found to afford sufficient ground for believing that the two diseases have been separated with a considerable degree of accuracy, then a comparison of the course and symptoms in the two series may be expected to furnish us with some useful data for their clinical diagnosis. They may be conveniently considered in the same order as in the typhoids.

The qualifying term "acute" malarial remittents is used above in order to exclude cases of chronic malarial fever—best designated by the valuable old, but comprehensive term, malarial cachexia (which workers in the malarious parts of India desire to see restored to the official nomenclature of the Royal College of Physicians),—for in these

also the remittent type of fever occurs now and then interspersed in the generally intermittent course of the disease. As I have recently showed elsewhere (8), there are certain special blood changes of great importance found in such cases—namely, an extreme reduction in the total number of the white corpuscles, accompanied by a great relative reduction in the polynuclears, with a corresponding increase in the percentage of the lymphocytes as well as the typical increase of the large mononuclears of acute malaria if marked fever is present. These changes are of great prognostic value, and I have suggested that they may explain the great resistance of such cases to ordinary doses of quinine, and also the success I have recently had with very large ones by the mouth or the hypodermic use of the drug in chronic malaria. Interesting as this class of cases are, they fall beyond the scope of the present paper, for they cannot well be mistaken for typhoid or other "continued" fevers.

Age-incidence.—This is shown in the following table:

Table of Age-incidence.

Years .	5-10	11-15	16-20	21-25	26-30	31-40	Over 40
Cases .	2	3	10	4	6	3	1

This shows a very similar incidence to that of typhoid fever, so that no diagnostic import attaches to the ages of the patients in the case of these two fevers.

The duration of the fever.—This is of much greater importance, for we have seen that typhoid very rarely runs a course of much under three weeks. In the following table the total duration of the fever both before and after admission is given in the first line, and the time the fever lasted under treatment in the hospital, where quinine was always given in smaller or larger doses, is shown in the second line.

Table of Duration of Fever.

Duration of fever in days . . .	1-7 .	8-14 .	15-20 .	21-25 .	26-30 .	31-40 .	Over 40
Total duration . . .	3 .	8 .	8 .	2 .	4 .	1 .	3
Fever in hospital . .	12 .	11 .	3 .	2 .	1 .	— .	—

Here we see a marked difference from typhoid fever, the duration of which exceeded twenty days in four fifths of the cases, and in only 4 per cent. ended within two weeks. Still more marked is the difference in the duration of the fever after coming under treatment, for the majority of the typhoid cases were admitted during the first week of the disease, and therefore had two weeks or more fever in hospital; while in the case of the malarial remittents under treatment with quinine, almost four fifths came to an end within fourteen days of admission, and over one third within one week. This is in agreement with the conclusion I came to over a year ago (7) with regard to continued and remittent fevers in natives (excluding cases of malarial cachexia)—namely, that upwards of 80 per cent. of such fevers which lasted three weeks or more were typhoid fever.

Clinical characters.—The chief points in which acute malarial remittents differ from typhoid are mainly of a negative character. Thus in the former, diarrhoea, abdominal distension and pain, rose-spots, and bronchial catarrh are absent or rarely met with. Haemorrhage from the bowel is very rare, except when dysentery complicates the disease. On the other hand, the spleen is much more frequently and markedly enlarged in the malarial remittents, and the liver is also frequently to be felt below the ribs. A history of chill or rigors or fever on and off for some time previously is in favour of a diagnosis of malarial remittent fever, but it is also not very rarely obtained in cases of typhoid in the tropics, so cannot be relied on very much.

The temperature curve.—This is of great importance, for although the remittent type is commonly seen in

typhoid, yet the rises and falls are as a rule much more regular and punctual to the hour in malarial remittents, and also usually of greater amplitude. When the rises occur regularly at some other period of the twenty-four hours than the afternoon or early evening, the case is nearly certain to be malarial. Of even greater value is the fact that in all my charts I can only find one malarial remittent fever in which the temperature remained within two degrees for upwards of forty-eight hours, and at a height of above 101°F ., unless there was some complication such as pneumonia. Every other case in which this continued type of a high degree was present proved to be enteric fever and not malarial. Of course a similar type is common in pneumonia, but here the presence of leucocytosis will exclude uncomplicated typhoid. As this continued type is most frequently seen during the first and second week of typhoid it is of very great diagnostic value, and has frequently enabled me to correctly diagnose typhoid fever in an early stage of the disease, before other definite symptoms were present; and I look on the establishment of this point, by means of my study of a large number of four-hour charts of continued and remittent fevers controlled by serum and blood tests, as a most important practical outcome of this investigation. The contrary, of course, does not hold good, for, as we have seen, the curve in true typhoid may be remittent, or even rarely intermittent, and may also occasionally show as great regularity of the remissions as in malarial cases. There remain, then, a number of cases in which the temperature curve will not be of any material service, and it is in these that the serum tests and leucocyte counts are of such great value.

The pulse-rate.—It is a well-known feature of typhoid fever that the pulse may remain below 100 per minute persistently for days when the temperature is raised to 103° or 104°F ., especially in cases which are running a favourable course. A large proportion of my cases have shown this point in a well-marked degree. On the other

hand, I can only find one chart, out of a number in which the pulse-rate was recorded, in which it remained persistently below 100 per minute in malarial remittent fevers, and this was a very mild one in which the temperature never rose above 101.2° . This slow pulse-rate when present is a valuable point in favour of typhoid as against malarial remittent fever, while it is most frequently seen in the mild cases, which are most difficult to diagnose by purely clinical means.

The malarial parasites.—As already mentioned, all the cases here dealt with had been saturated with quinine for some days before I was able to examine them, so that the parasites were seldom found in the single slide made on the one or, rarely, two occasions when the blood was tested. When present they were always of the malignant tertian variety, but out of the twenty-nine cases referred to above, in only six of them, or 20.7 per cent., were they detected, Romanowsky's stain being always used. This agrees closely with Captain Delany's results in the Medical College Hospital, Calcutta, under very similar circumstances (3). In two cases, however, the temperature had finally reached normal before they were examined, and in three more it was on its final fall. If these are excluded as extremely unlikely to show parasites, then they were found in 25 per cent. of the remaining cases.

The serum reaction, as already mentioned, was negative, except in one man, who had typhoid fever two years before. That for Malta fever was also negative, except that in one or two cases a clumping in a dilution of only 1 in 10 occurred, as happens occasionally, in my experience, in normal bloods and in those of persons suffering from various diseases other than Malta fever (9).

The large mononuclear increase in malarial remittents.

—The following table shows the percentage of large mononuclears found in thirty-four examinations of the blood, arranged in the same way as that already given for typhoid cases, except that they are classed in accordance

with the temperature when the film was taken instead of the week of the disease,—the former having an important influence, for, as shown by Drs. Christophers and Stephens (5), the large mononuclear increase becomes less marked as the temperature rises.

Table of Large Mononuclear Increase in Malarial Remittent Fevers.

Percentages	Normal or slightly increased, 4.			Markedly increased, 30.			Total.
	-4	4-8	8-11	11-15	15-20	Over 20	
Temp. - 101° F.	0	2	1	7	7	4	21
Temp. + 101° F.	0	1	0	8	3	1	13
	—	—	—	—	—	—	—
Total	0	3	1	15	10	5	34

We see from this table that in only four out of thirty-four examinations were the large mononuclears less than 11 per cent., and in one of these they were increased over that number at a second examination when the temperature had fallen to normal. This is just the reverse of what we found to be the case in typhoid, in only two cases of which during the first three weeks of the disease were over 11 per cent. large mononuclears found, and these were complicated by malaria; so that by the leucocyte count alone the two forms of remittent fever can almost invariably be differentiated. It will also be observed that the highest percentages of large mononuclears are met with in examinations made when the temperature is below 101° , as compared with those made when it is above that point, which is in accordance with the observations of other workers on malaria, as mentioned above.

Table of the Lymphocytes in Malarial Remittent Fevers.

Percentages Number of ex- aminations	Normal, 23.					Increased, 11.					Total.
	-20	20-25	25-30	30-35	35-40	40-50	50				
	7	8	8	4	3	3	1	34			

From this table we see that more than two thirds of the cases showed no increase of the lymphocytes, while a marked increase was quite exceptional, instead of being the rule, as in typhoid. These two points taken together are of very great value in the differential diagnosis of the two fevers, and will very rarely indeed mislead, if the precaution is taken of examining the blood in the morning during a remission of the fever in cases suspected to be malarial, for it is at the time that the increase of the large mononuclears is best marked.

The quinine test.—Before leaving the subject of the malarial remittent fevers we must discuss how far the diagnosis of malarial remittents made by means of the differential leucocyte counts has been borne out by the results of subsequent antimalarial treatment, for unless they will stand this test in patients not yet the subject of marked malarial cachexia, they cannot be relied on. Now in several of these cases the patients had been taking quinine in 10-grain doses three times a day by the mouth for a week or more, with little or no effect on the temperature curve; and this would be held by some to be sufficient to prove that they were not of a malarial nature. This opinion may be true of malaria in some countries, but it is utterly untrue of many cases of malaria as seen in Lower Bengal and other parts of India—a point on which I cannot lay too much stress, as this fallacy has been responsible for much lingering fever and many deaths. During the last fever season at the Calcutta (General Hospital), as soon as a large mononuclear increase has been found in cases which have resisted quinine by the mouth, the drug has been given hypodermically in from 5- to 10-grain doses twice a day, the bi-hydrochlorate being used, and injected into the subcutaneous tissues. The results have been admirable, for case after case has fallen to normal in two or three days, some of the charts of which I shall show you presently (Cases 8 to 10). The leucocyte count, then, has come triumphantly out of the ordeal of the quinine test, although in most of these cases no

parasites could be found in the peripheral circulation, and fortunately no opportunity of finding them after death has occurred, although a few years back post-mortems were not very rare in this class of cases, especially when quinine was ordered to be only given when the temperature was below a certain point, with the result that the drug was reduced in direct proportion to the severity of the case, instead of being increased.

Are there any continued or remittent fevers other than typhoid and malarial?—As already mentioned, this investigation was started with the object of separating out the known fevers with a view to studying the undifferentiated ones described clinically by Crombie and others, with whom I quite thought that such existed. So far I have dealt with fifty typhoids and twenty-nine acute malarial remittents. In addition to these, six chronic malarial remittents and eleven more malarial intermittents are included in my European series, making a total of ninety-six cases out of the 126 cases examined in the General Hospital. Among the remaining cases we first have a miscellaneous assortment, including cases of phthisis, pneumonia, cerebro-spinal fever, liver abscess, cellulitis, and other local inflammatory conditions, all showing varying degrees of leucocytosis, which in several cases materially assisted the diagnosis. For example, in one case malarial parasites were believed to have been found by the medical officer in charge, but the fever increased steadily in spite of hypodermic injections of quinine, and I was asked to examine the blood. Finding leucocytosis (13,000) and pain over the liver and in the right shoulder, I diagnosed liver abscess, but the supposed parasite had greater weight than the leucocyte count, and the patient was sent on a voyage to Colombo, where his liver abscess was successfully opened. In another case a child suffered from an obscure fever, and two examinations of the blood failed to reveal any evidence of either malaria or typhoid, the case soon after developing into one of tabes mesenterica. In two other cases an irregular fever with some degree of

leucocytosis accompanied dysentery, probably of the amoebic type.

When all the above well-known diseases are excluded, what have we left in the way of continued fevers? Practically nothing. Some three or four cases, all in the first twenty examined, when my experience was very limited, remain; and looking at the notes and charts of these in the light of my present experience, I cannot find one which repeated examination would not in all probability have proved to have been either typhoid or malarial. One of these I thought at the time might correspond with the type which Dr. Patrick Manson describes under the term double continued fever, but I have since seen very similar cases which proved to be malarial, and yielded to full doses of quinine. In my last 100 cases I have met with very few doubtful ones, and none which I have any good reason for thinking might be a new and undifferentiated fever, disappointing as it is to have to say so. What, then, are the cases described by Crombie as new continued fevers?

"SIMPLE CONTINUED FEVER."

Dr. Crombie holds that three quarters of the cases which are wrongly returned under the head of ague belong to the class he terms "simple continued fever." He describes them as often ushered in with a rigor, followed by high fever, with headache and gastric disturbance, and lasting from three to eight days; but sometimes resembling a mild typhoid and going on for two, three, or four weeks, in which case he calls it "Calcutta fever." They are most commonly attributed to "exposure to the sun." Now the year Dr. Crombie's address before the Indian Medical Congress on Fevers was published I undertook an investigation of a hundred consecutive fever cases in a native regiment stationed in Chota Nagpur; and a microscopical examination of the blood and an analysis of the symptoms convinced me that they were all malarial.

"Simple continued fever," however, has been very commonly diagnosed in the Calcutta General Hospital by those who had the advantage of studying there under Dr. Crombie himself, and several cases quite typically as he describes them, which had been diagnosed under this term, are included in my table of cases. Each of them showed the large mononuclear increase of malaria; several showed a typical tertian character, and they were each cured with quinine; a chart of one will be shown presently (Case 7). I have not yet had an opportunity of examining these cases immediately on admission before they had taken quinine, so am not prepared to state positively that there are not non-malarial fevers of this type; but if so, I am certain they are not anything like as common as Dr. Crombie holds, but hope to be able to further investigate this point before very long. In the meantime some light may perhaps be thrown on the subject by a comparison of the seasonal incidence of the cases returned as simple continued fever and as malarial intermittent fever respectively; for if they are quite different diseases, and especially if the former is commonly due to exposure to the sun, this should be quite different, for the malarial season in Calcutta is the rainy one, when the sun is seldom seen. In the lowest part of the accompanying diagram the cases returned under these two heads month by month during the last three years are shown, the malarial intermittents being represented by the uninterrupted lines, and the simple continued fevers by the broken ones. I find it has been more or less the custom in this hospital to look on short fever cases with any enlargement of the spleen as undoubtedly malarial, and of those without any enlargement as being very probably "simple continued fever," especially if there was no history of chill or rigor. Now one of the first things which strikes a medical man on going to India is the frequency with which typical ague is absent in purely malarial fevers, especially malignant tertians. Further, in first attacks, which will be most frequent at the beginning of the fever season, the spleen will not

yet be enlarged. Malarial intermittents without spleen enlargement will occur in greatest numbers at the beginning and be fewest at the end of the malarial fever season, when they will more frequently show an enlarged spleen due to repeated attacks of the disease. If now we examine the chart of the cases diagnosed under these two headings for the years 1900 and 1901, we see that in both years the two coincide very closely, both in monthly incidence and in number, the only difference being that in the first year the curve of the so-called "simple continued fevers" both rose and fell a month earlier than the malarial cases; this being precisely what might have been expected if all the cases were really malarial in nature, but those without enlargement of the spleen had more frequently been wrongly called "simple continued fever." During the year 1902 it will be observed that this supposed new fever has nearly completely disappeared, especially during the malarial fever season; this change having closely coincided with the promotion to higher spheres of some of the medical officers who had worked under Dr. Crombie, while at the same time greater attention has been paid to the use of the microscope in the diagnosis of the fever cases. This agrees with my former conclusion that nearly if not quite all of these short fevers are malarial in nature, and that "simple continued fever," if it exists at all, is an uncommon disease, and should not be diagnosed until malaria has been excluded by an examination for malarial parasites, or, if quinine has already been taken, also for the large mononuclear increase. It is also worthy of note in connection with the supposed relationship between "simple continued fever" and "exposure to the sun," that the cases returned under this head are fewest during the dry, hot months of March to May, and greatest in the cloudy months of the rainy season. The existence of "simple continued fever" as a separate specific disease still remains to be proved.

"NON-MALARIAL REMITTENT FEVER."

Next we come to the fever which Crombie describes under this term, and which he regards as the most important tropical fever whose specific organism awaits its discoverer. It has been a great disappointment to me not to have been able to find this fever to exist at all, as I believed it did when I began this investigation; but on reading over again Dr. Crombie's description of the disease, the mistake into which he has fallen is quite easy to understand in the pre-Widal and leucocyte-count days. To make the matter clear it will be necessary to quote from his writings on the subject, bearing in mind his statement that true typhoid fever is very rare in natives of India, and that only three cases were returned as such in the large Medical College Hospital in the ten years 1880-89. He summarises his description of it in these words:—"This condition, one of persistent high temperature without any marked remission, a distinctly enlarged and congested liver with bilious diarrhoea, a congestion of the back of both lungs, and a low muttering delirium, is generally reached by the eighteenth to the twenty-fourth day. If coma supervenes the patient frequently dies at this period." He also states that quinine has no effect on the fever, and that, although he has seen it in Europeans, yet "it is essentially a disease of natives, and is not common after thirty years of age." With the exception of the absence of the yellow stools of typhoid in Europeans, no doubt owing to the vegetarian diet of most poor natives, this appears to me to be as good a description of typhoid fever as I have seen; yet it is prefaced by the remarkable statement that the fever "is by some considered to be a variety of typhoid fever notwithstanding its divergence from all the symptoms of that disease!" It agrees absolutely with the large number of cases of typhoid in natives verified by Widal's test during the last eighteen months in the Medical College Hospital. Further, every such case with the continued type of fever and the absence of

pneumonia, etc., in this hospital has proved on blood examination to be typhoid, so unless Dr. Crombie's fever has disappeared and typhoid taken its place in the last few years, there can be no doubt that his "non-malarial remittent fever" so commonly occurring in natives, who according to him are nearly completely immune to typhoid, is nothing but typhoid in natives.

As already mentioned, I have not been able to find any case of such a continued fever as Dr. Crombie describes in the European General Hospital which has not proved to be either typhoid or malarial. It is worthy of note that he mentions that in his supposed new continued fever "the temperature is generally very high, touching 104° and 105° for a long part of its course, the daily fluctuations not exceeding 2° to 2.5° F." Now we have seen that all such cases have been proved by the serum test to be typhoid. This question may also be examined in the light of the seasonal incidence of typhoid as opposed to all other continued and remittent fevers, including malarial remittents. The middle curve of the diagram already referred to shows all the latter cases, and the top one all the typhoid cases, for the last three years in the European General Hospital. The maximum typhoid season is a very definite one, being reached in each year in the dry cold weather and hot weather months (for we have no spring in Bengal) in the first five months of the year, and thus corresponds with the minimum malarial fever season. In the first two years charted there is also a slighter rise in the curve in the rainy malarious months, but this is absent in the last year, when the serum test was regularly used. It would, however, have appeared as usual had not several cases, which had originally been diagnosed as typhoid, been proved by the blood examinations to be malarial remittents. The rainy season small rises of the first two years were probably also due to a few malarial remittents having been wrongly diagnosed as typhoid fever. If now we turn to the curve showing all the other remittent fever cases (all truly continued ones having proved to be typhoid),

we find that the main rise in the curve each year is in the same months as those in which the malarial remittent fevers were most prevalent. This is in exact agreement with the conclusion I have arrived at by means of the blood tests—namely, that the only remittent fever other than typhoid is the malarial remittent. A few cases were returned as "simple continued fever," but they showed the remittent type, as defined in a previous section of this paper, and they also occurred most commonly during the malarial season. These curves of the seasonal incidence of the remittent fevers other than typhoid, then, strongly support the view that all such cases are malarial, and give no indication of the existence of any new undifferentiated fever in the tropics, the existence of which I now very gravely doubt.

LOW FEVER.

Although this is not, strictly speaking, a continued or remittent fever, but rather an intermittent one, yet as it is included under the former term by Dr. Crombie it may be briefly referred to in conclusion. I am glad in this case to be able to agree with him as to the existence of this as a clinically distinct fever, on which the few observations I have yet been able to make may, perhaps, throw a little fresh light. Dr. Crombie well describes it as "a persistent low elevation of fever temperature unaccompanied by any constant symptoms, of indefinite duration, and uninfluenced either by quinine or arsenic. The temperature never falls below 99° F., and rarely rises above 101.5° ." It is met with in Europeans, and causes much depression, and is generally cured by a change of climate or a sea trip. I have, however, several times known it recur on the patient's return to Bengal, even after long leave to England. In my experience also the rise of temperature is always in the afternoon, and never at other odd times, as not unfrequently happens in malaria. I have only had an opportunity of examining the blood in a few cases of this fever, but have always found a marked reduction in

the total number of leucocytes, accompanied by a disproportionate decrease of the polynucleans and a corresponding increased percentage of lymphocytes. Thus the total count may be from 2000 to 5000 per c.mm., while the polynucleans will be reduced to about 50 per cent, or even less, and the lymphocytes increased to 40 per cent, or even more. Now this is just the change met with in cases of malarial cachexia in the absence of active malarial fever, when the large mononuclear increase is not found. On the other hand, we know that when the general health is bad there is a tendency for a reduction of the polynucleans to occur, and it may well be that long-continued exposure to the debilitating influences of a tropical climate may produce an exaggerated condition of this nature. This weakness and want of resisting powers may lead to a loss of complete control by the heat-regulating centres, allowing the body temperature to rise with the afternoon increase of that of the surrounding atmosphere. Against this simple explanation is the fact that I have on two occasions known more than one member of a family affected by this form of fever, which might be held by some to indicate its being of a specific nature; but on the other hand, in one of these instances one of the two sufferers subsequently developed an attack of ordinary malarial fever. The curative effect of a change of air also points to its being a condition of debility rather than a specific fever; and although I am not prepared to dogmatise on the subject with such a small experience, I am inclined to think that the disease is climatic rather than specific, and that latent malaria may play a large part in its causation. With regard to treatment, I have seen the fever disappear, and at the same time the percentage of the polynucleans increase, while oil of eucalyptus was being given—a drug which was suggested to me as useful in increasing the leucocytes by Sir Thomas Lauder Brunton; but my cases are too few to allow me to say definitely that the drug has a curative effect on this form of fever, without further evidence.

MALTA FEVER.

This concludes the discussion of the different forms of continued fever which have been described as occurring in the tropics, with the exception of Malta fever. I have tested the blood of upwards of 100 continued and remittent fevers by the serum test with the Malta fever micrococcus, but with entirely negative results, with the exception of an occasional reaction in a dilution of 1 in 10 only, which I have given reasons elsewhere (9) for believing to be of no diagnostic value. I find records of cases in the General Hospital in sailors who have recently visited Mediterranean ports, so that our medical officers are familiar with the disease both from this and from their Netley experience; but I find they are nearly all agreed in considering that this disease does not occur indigenously in Lower Bengal, whatever it may do in North-West India. This statement is equally true of Assam in my experience, which is confirmed by that of Major Ronald Ross.

ILLUSTRATIVE CASES.

The twelve following cases have been selected to illustrate the most important points dealt with in this paper. The nature of the disease, the blood changes found, and the treatment have been entered on the four-hour temperature charts, so that they speak for themselves, and very little description is necessary.

Typhoid Fever.

CASE 1.—Clinically, a typical case of typhoid fever. Widal reaction negative on the 15th and 25th day. Lymphocytes increased to 38·2 on the 15th and to 47 per cent. on the 25th day, without any increase of the large mononucleans. The chart shows a continued type of the fever from the 9th to the 11th and up to the 13th and 14th

days of the illness, the temperature not having varied more than two degrees during that period.

CASE 2.—An abortive case of typhoid fever, which was not suspected to be such until a brother and sister were admitted for fever, and I found that all three gave a positive Widal reaction for typhoid, as did two more of the same family admitted shortly after. The fever in this case lasted only 14 days, yet the lymphocyte increase was very marked, 50·4 per cent. being found. In my experience these mild cases, as a rule, show it particularly well.

CASE 3.—This case precisely resembled No. 2, except that the reaction for typhoid was negative on the 7th and 21st days; but the lymphocyte increase was well marked, 48·8 per cent., on the second examination, the large mononuclears not being increased, so I am inclined to regard it as an abortive typhoid, or it may possibly belong to the class recently called paratyphoid. It was one of the very few doubtful cases in the series.

CASE 4.—This case is of interest from several points of view. Clinically, it was for some time regarded as malarial in nature. On examining the blood on the 9th day the Widal reaction was negative, but the lymphocytes numbered 39·6 per cent. without any increase of the large mononuclears, and I diagnosed the case as typhoid on the strength of the leucocyte count. On the 18th day a second examination was made, and now a positive Widal reaction for typhoid was obtained, while the leucocyte count remained practically the same, my diagnosis in the early stages thus being confirmed. I have met with other cases in which I have correctly diagnosed typhoid fever by the leucocyte count before the appearance of the serum reaction, the latter having given a positive result at a later stage of the disease. Another point of interest is the intermittent type of the fever, the

patient having been a child, in which this type is not very rare in typhoid fever.

CASE 5.—A typical very severe case of typhoid, which proved fatal on the 19th day. It shows well the "continued type" of fever, and also illustrates the absence of the lymphocyte increase in very severe cases, which has already been mentioned as being of prognostic value.

CASE 6.—A case of typhoid fever complicated by malaria admitted late in the disease, and giving a serum reaction in a dilution of 1 in 100. The leucocyte count showed 18 per cent. of large mononuclears, which raised a suspicion of malaria, and after some search a few malignant tertian malarial parasites were found. During convalescence a typical attack of malarial fever also occurred. The typhoid symptoms were severe and the temperature of the "continued type," while the lymphocytes showed no increase during the height of the fever.

Malarial Remittents.

CASE 7.—A case of remittent malarial fever showing well-marked fall of temperature every other day, and an increase of the large mononuclears to 16·4 per cent., and yielding to quinine in 5-grain doses every four hours. The case was diagnosed at first as one of "simple continued fever," and I have seen other similar cases which proved on examination with the microscope to be malarial in nature.

CASE 8.—A case of severe malarial remittent fever yielding rapidly to quinine hypodermically. This is the only malarial case I have yet met with in which the temperature remained within two degrees Fahrenheit for two days. Note that at the first examination of the blood, when the temperature was high, 12·4 per

cent. of large mononuclears were found; but three days later, when it had fallen to normal, they numbered 28 per cent.

CASE 9.—A typical case of a malarial remittent fever rapidly cured by the hypodermic use of quinine after the failure of the drug in 10-grain doses three times a day by the mouth. No parasites could be found when the blood was examined four days after admission, when much quinine had been taken, but 15.6 per cent. of large mononuclears were present, which enabled a correct diagnosis to be made.

CASE 10.—Another case of malarial remittent fever diagnosed by the large mononuclear increase, in spite of a positive reaction for typhoid fever due to a severe attack of the disease in South Africa two years before, and successfully treated by hypodermic quinine.

CASE 11.—Another malarial remittent with 21.2 per cent. of large mononuclears and scanty malignant tertian parasites, rapidly cured with quinine hypodermically after failure of the drug by the mouth.

CASE 12.—A case of malarial fever showing a double daily rise of temperature, and very resistant to treatment with quinine. The large mononuclears numbered 16.4 per cent. The patient left hospital unrelieved. No parasites were found on the single occasion when the blood was examined, after much quinine had been taken. These cases of double daily rise are in my experience particularly difficult to treat, and they deserve closer examination.

CONCLUSION.

The general conclusion arrived at by the careful clinical and pathological study by modern blood tests of a large

and consecutive series of continued and remittent fevers in both Europeans and natives in the hospitals of Calcutta, then, is that only two forms exist, at any rate of long duration—namely, typhoid and malarial remittents. Further, these can be distinguished in a considerable proportion of the cases by purely clinical methods, of which the temperature curve and pulse-rate, and presence or absence of abdominal symptoms, and the action of quinine, are the most important. The remainder can be differentiated by the serum test or by the differential leucocyte count in all but a very few exceptional cases, the leucocyte count being of special value in the tropics on account of its being available when parasites are absent as a result of previous quinine treatment, and its not requiring a laboratory, which are very few and far between in the tropics at the present time; while it also has some prognostic value.

"Simple continued fever," if it exists at all as a separate entity, which still remains to be proved, is very rare indeed as compared with malarial fevers. The so-called "non-malarial remittent" in natives has been shown by the serum test to be nothing but typhoid fever. Low fever is distinct clinically, but is probably the result of the debilitating influences of prolonged residence in a tropical climate, including latent malaria, and not a new specific fever. Malta fever does not occur, or at least is exceedingly rare, in Lower Bengal and Assam.

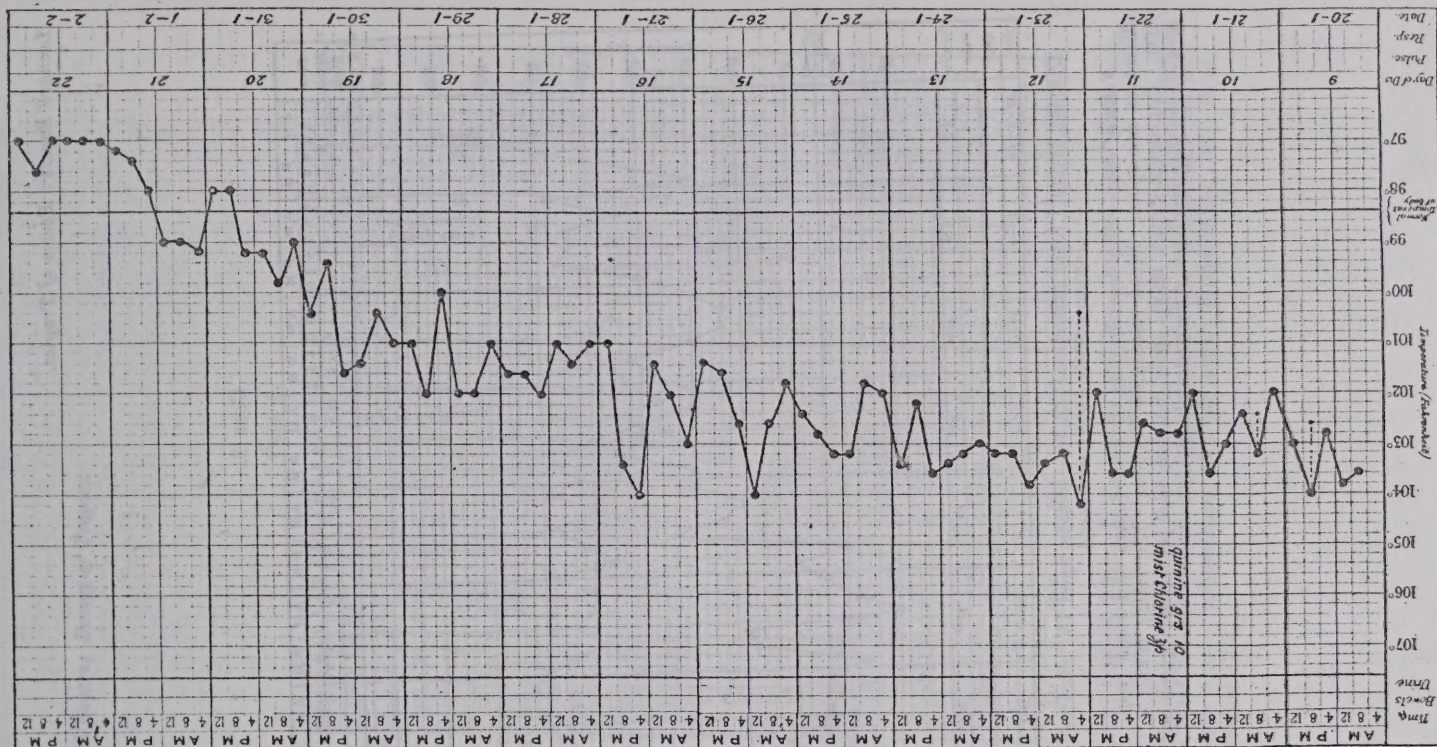
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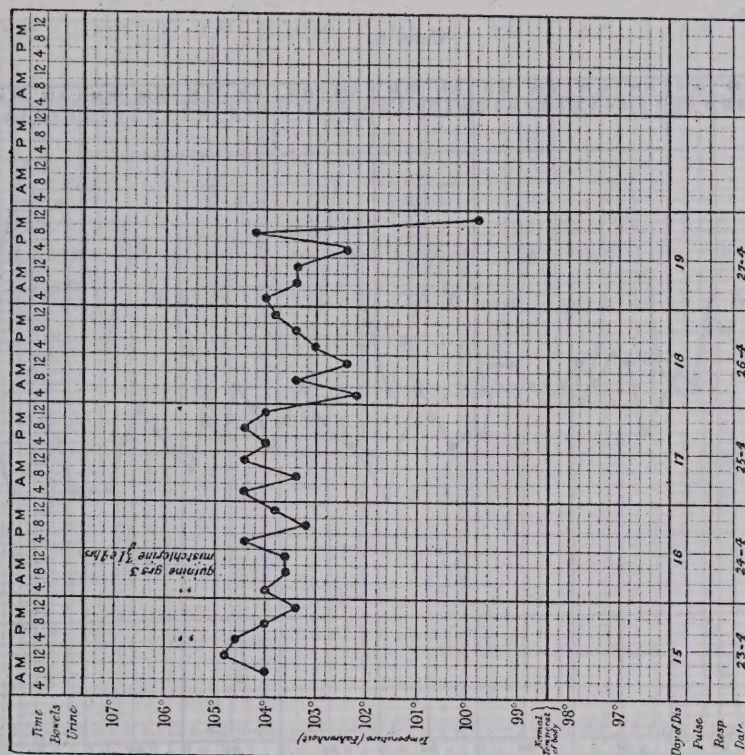
CASE I.



Disease, typhoid fever; J. T., male, aged 24; admitted January 20th, 1902; recovered.

Notes of case.—Clinically typhoid fever, but Widal reaction negative throughout. 15th day—Blood examination, January 26th; Widal for typhoid, -1 in 20; Widal for Malta fever, -1 in 10. Leucocyte count: polymorphs, 38.2; large mononuclears, 3.4; eosinophiles, 0.2; lymphocytes, 47.0; large mononuclears, 4.2; eosinophiles, 1.0.

CASE 5.

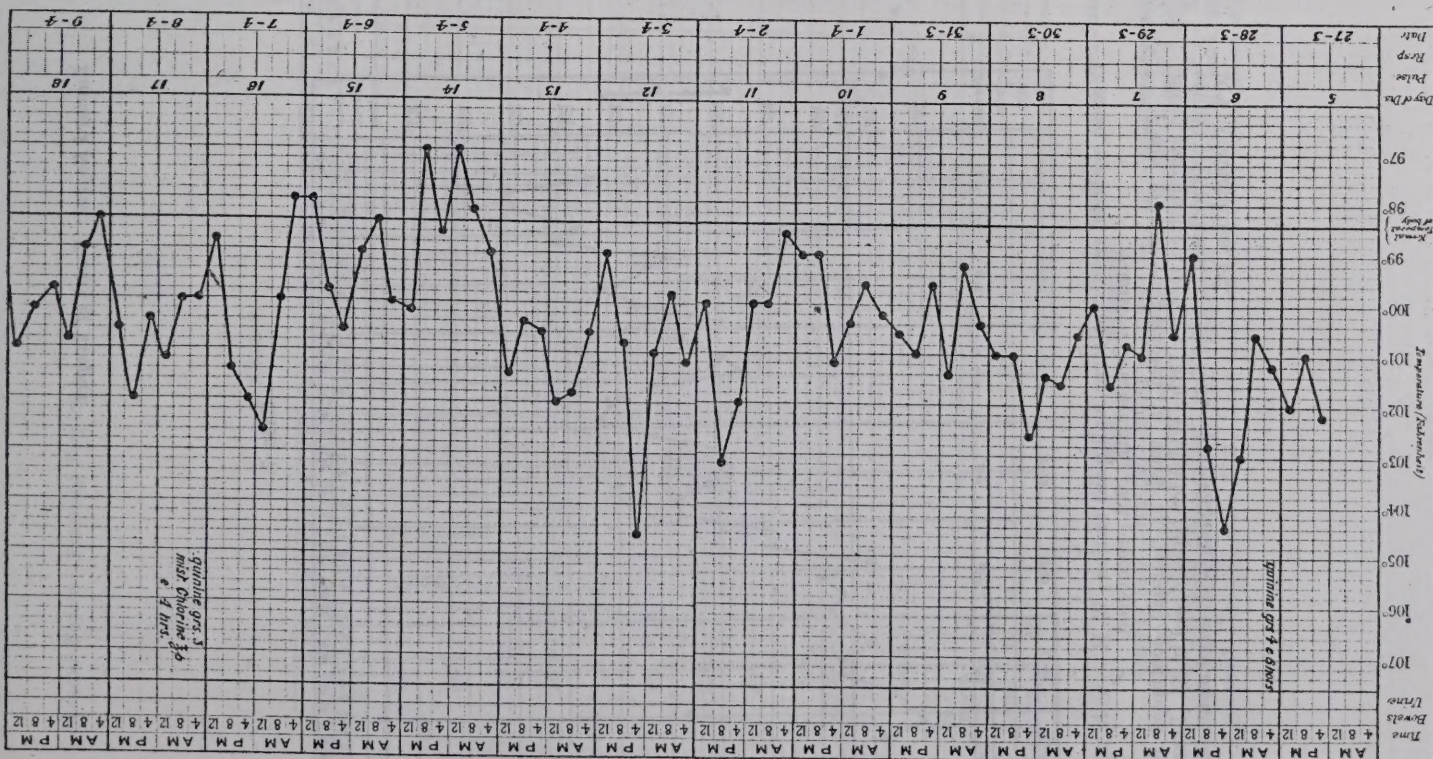


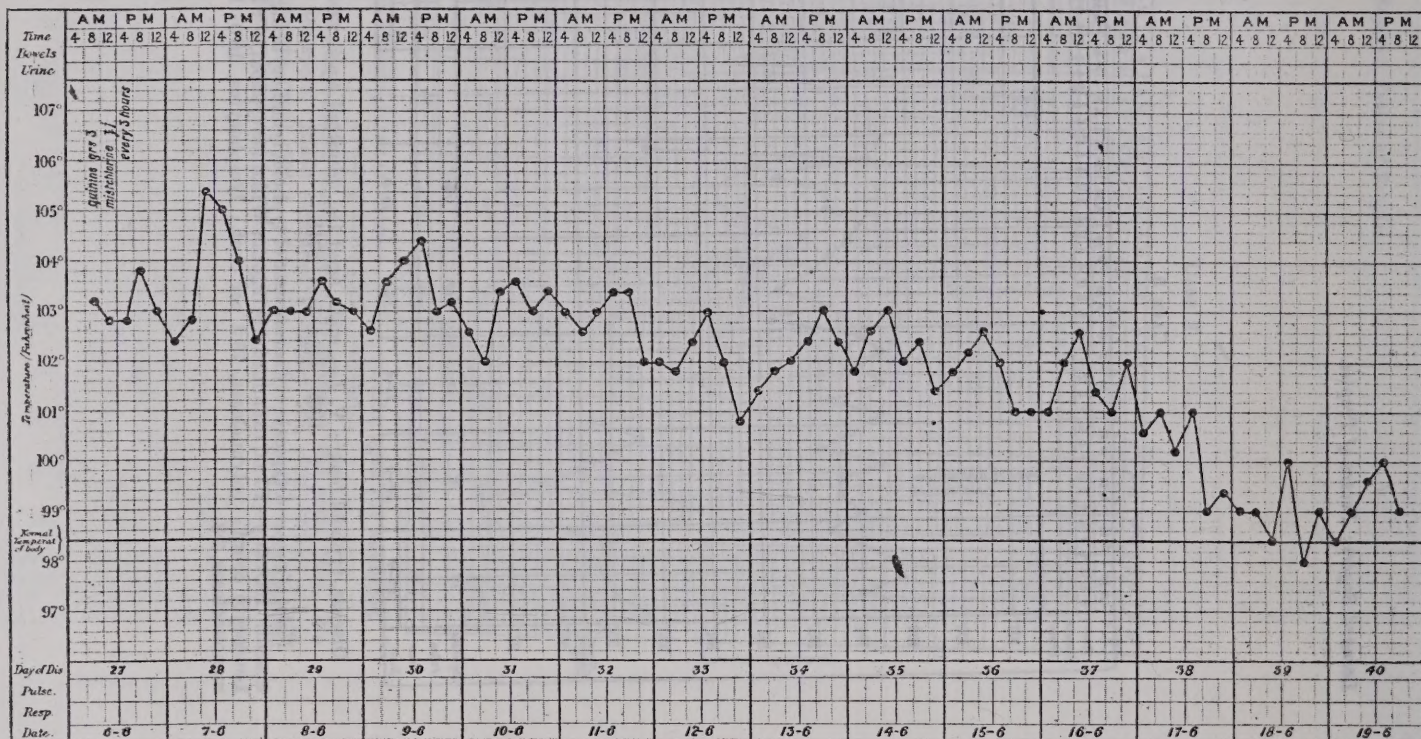
Disease, typhoid fever; V. J—, male, aged 18; admitted April 23rd, 1902; died April 27th.

Notes of case.—A typical very severe case of typhoid, lymphocyte increase absent. 18th day.—Blood examined April 26th; Widal for typhoid, + 1 in 40. Leucocyte count: polynuclears, 79·2 per cent.; lymphocytes, 18·0; large mononuclears, 2·8.

Notes of case.—Thought to be malarial at first. Lymphocyte count: 56·4 per cent.; lymphocytes, 39·6; large mononuclears, 3·2; eosinophiles, 0·1. 9th day—Blood examined March 31st; 9th; Widal, +1 in 40. Leucocyte count: polymorphs, 56·8 per cent.; lymphocytes, 40·0; large mononuclears, 2·8; eosinophiles, 0·4. 18th day—Blood examined April 1st; Widal, —1 in 20. Leucocyte count: polymorphs, 55·4 per cent.; lymphocytes, 39·6; large mononuclears, 3·2; eosinophiles, 0·1. 9th day—Blood examined March 31st; 9th; Widal, +1 in 40. Leucocyte count: polymorphs, 56·8 per cent.; lymphocytes, 40·0; large mononuclears, 2·8; eosinophiles, 0·4.

Disease, enteric fever; H. H.—, male, aged 9; admitted March 27th, 1902; recovered.

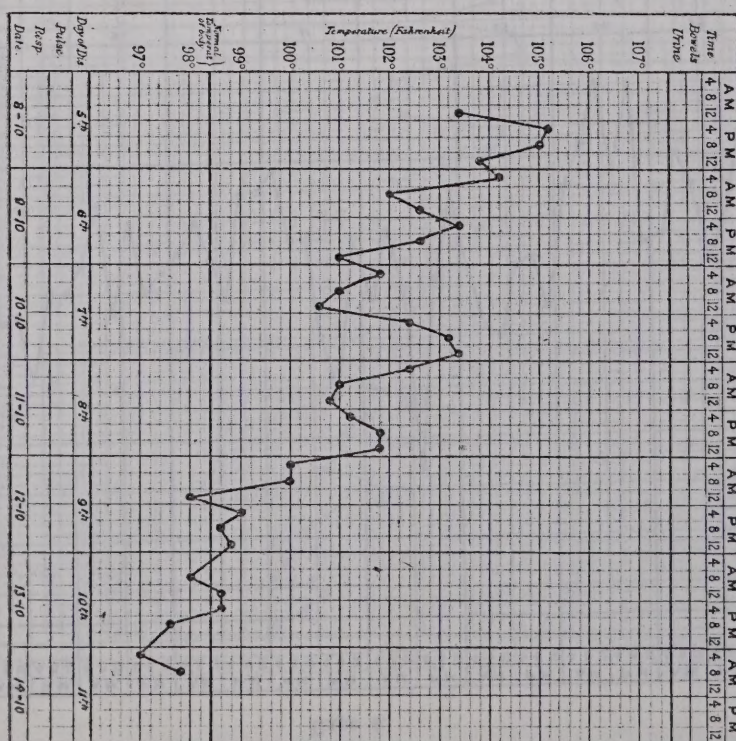




Disease, typhoid fever with malaria; Miss B—, aged 26; admitted June 30th, 1902; recovered.

Notes of case.—Blood examined May 7th and 13th. Widal for typhoid, +1 in 100. Leucocyte count: 28th day—Polynuclears, 60.8 per cent.; lymphocytes, 21.2; large mononuclears, 18.0. 34th day—Polynuclears, 73.2 per cent.; lymphocytes, 14.2; large mononuclears, 11.6. May 7th.—Malignant tertian malarial parasites found.

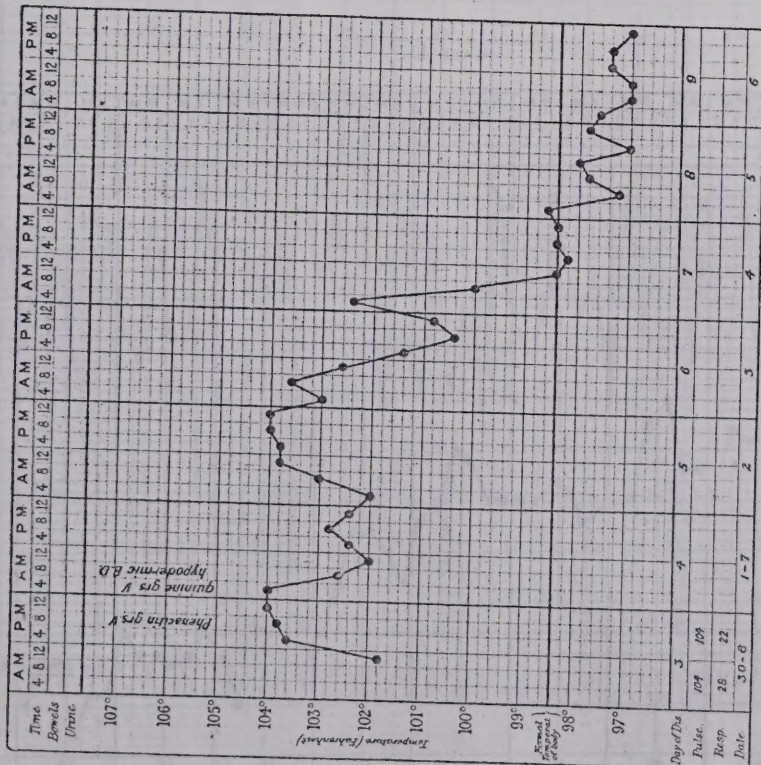
CASE 7.



Disease, malarial remittent fever, malignant tertian; W. H—, male, aged 17; admitted October 8th, 1901; recovered.

Notes of case.—Diagnosed in ward as "simple continued fever." Blood examination, October 18th; Widal for typhoid, —1 in 20. Leucocyte count: polynuclears, 60.4 per cent.; lymphocytes, 32.0; large mononuclears, 16.4; eosinophiles, 1.2.

CASE 8.

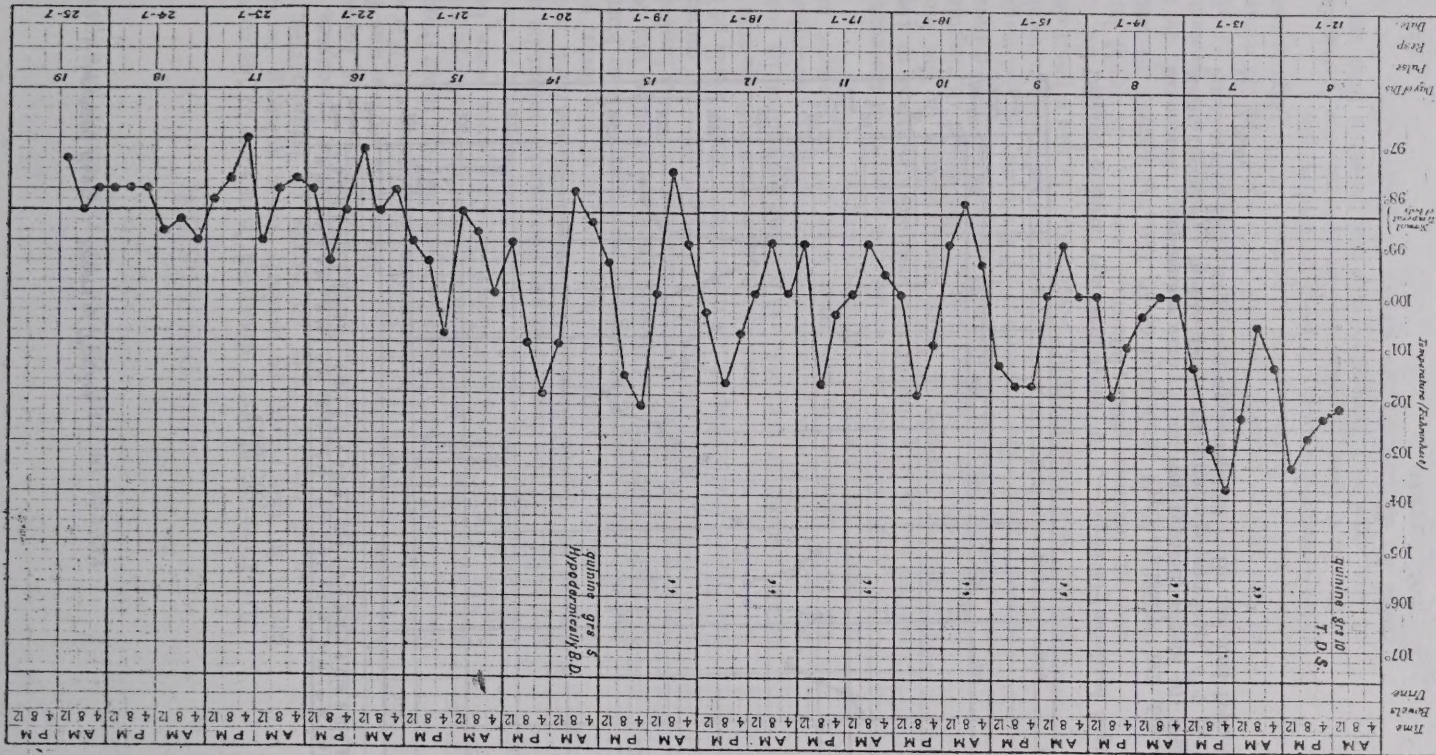


Disease, malarial remittent fever; M. J—, male, aged 20; admitted June 30th, 1902; recovered.

Notes of case.—4th day—Blood examined July 1st; Widal for typhoid, — 1 in 20; Widal for Malta fever, — 1 in 10. Leucocyte count: polynuclears, 63.2 per cent; lymphocytes, 24.4; large mononuclears, 12.4. 7th day—Blood examination, July 4th. Leucocyte count: polynuclears, 48.8 per cent; lymphocytes, 27.2; large mononuclears, 23.0; eosinophiles, 2.0.

Leonard Rogers: Fevers of Tropics.

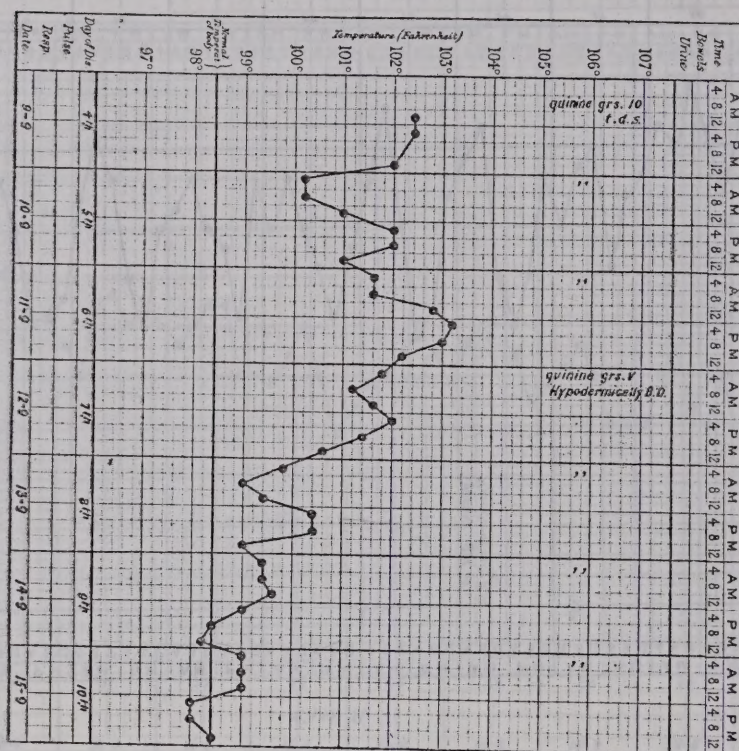
CASE 9.



Notes of case.—Cured by hypodermic injection of quinine after the failure of the drug by the mouth. 9th day—Blood examination, July 16th; Widal for typhoid, — 1 in 20; Widal for Malta fever, — 1 in 10. Leucocyte count, very few; polynuclears, 35.6 per cent; lymphocytes, 49.0; large mononuclears, 15.5; eosinophiles, 0.8.

Disease, malarial remittent fever; R. F—, male, aged 28; admitted July 12th, 1902; recovered.

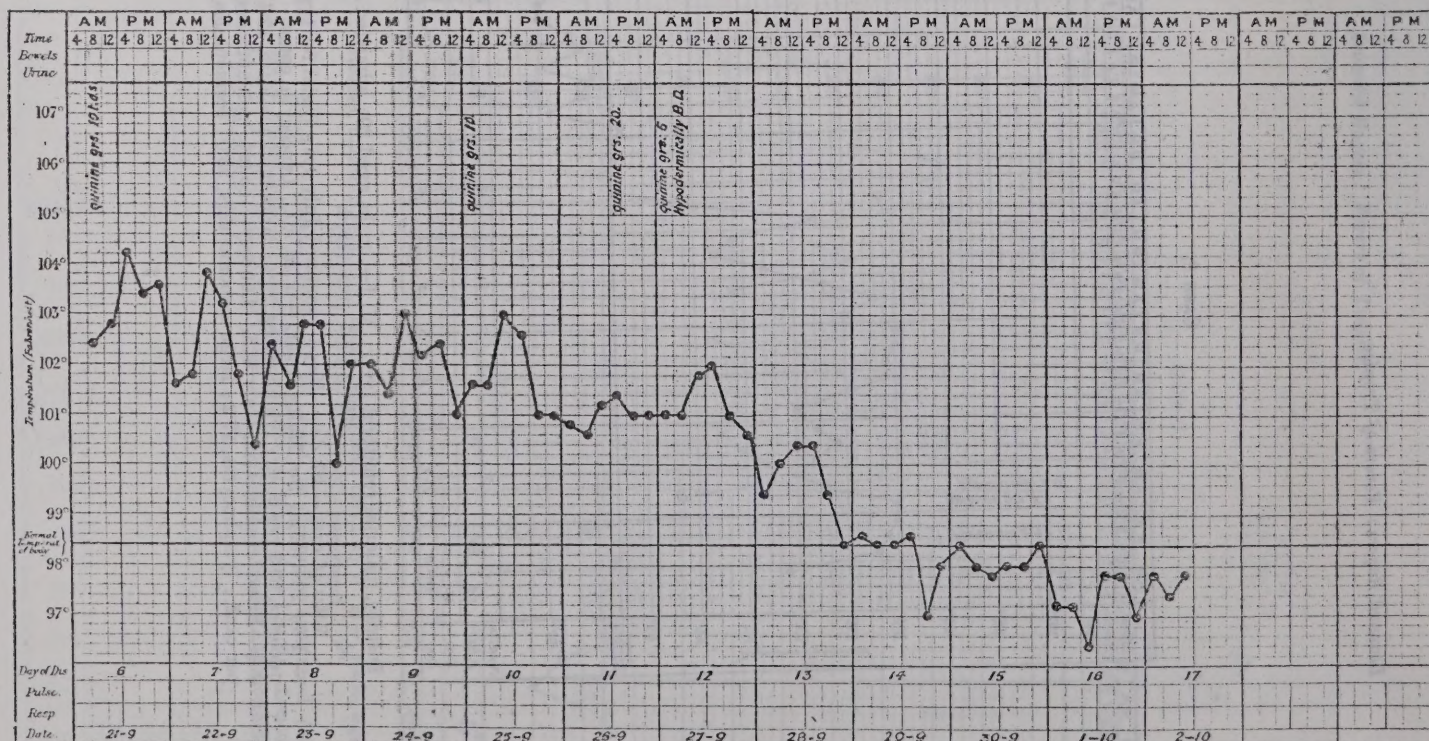
CASE 10.



Disease, malarial remittent fever; C. L., aged 30; admitted September 9th, 1902; recovered.

Notes of case.—Cured by quinine hypodermically, 6th day.—Blood examination, September 11th; Widal for typhoid, + 1 in 40; Widal for Malta fever, - 1 in 10. Leucocyte count: polynuclears, 47.6 per cent.; lymphocytes, 37.6; large mononuclears, 14.8. He had had typhoid two years ago.

CASE 11.



Disease, malarial remittent fever; L. A., male, aged 30; admitted September 21st, 1902; recovered.

Notes of case.—Cured by hypodermic injections of quinine after the failure of the drug by the mouth. 13th day.—Blood examination, September 25th; Widal for typhoid, - 1 in 20; Widal for Malta fever, - 1 in 10. Leucocyte count: polynuclears, 48.0 per cent.; lymphocytes, 30.8; large mononuclears, 21.2.

DISCUSSION.

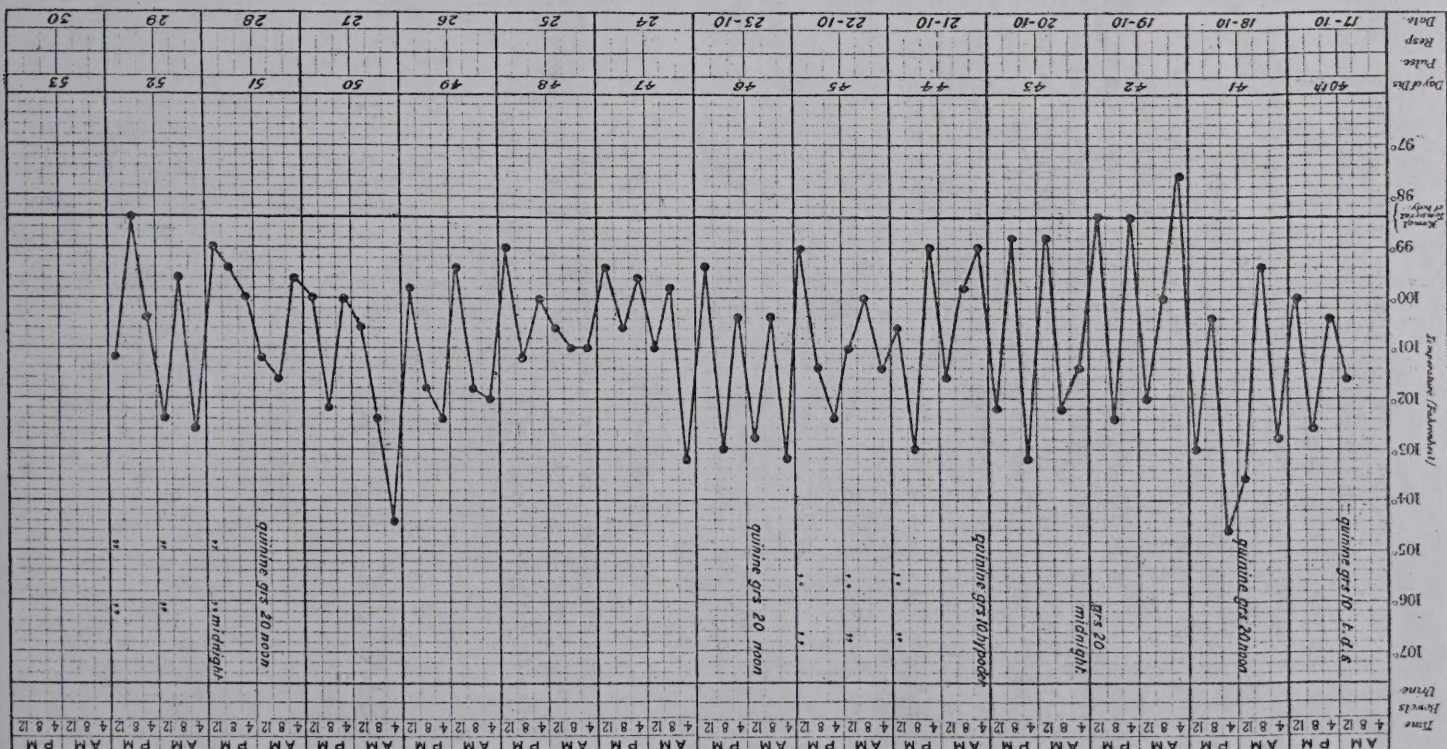
Dr. PATRICK MANSON dissented from some of the conclusions drawn in the paper, particularly those relating to the diagnosing of typhoid from an excess of lymphocytes, and of malaria from an excess of large mononuclear leucocytes. Other fevers besides malaria showed the latter excess; as, for example, the fever of trypanosomiasis. When this excess was found it might be concluded that malaria might be present; if it were not found, that it was not present;—a very different thing from saying that an excess of large mononuclears was pathognomonic of malaria. The deductions drawn in the paper were based on Calcutta experience, but this could not be extended to the tropics generally. If the diseases of any one country might be taken as typical of tropical disease, that country was Africa, not India. In regard to the possibly malarial nature of the fever, which he had described many years ago, he said that while in Formosa he had great belief in the specific value of quinine, but when he went to Amoy and encountered this disease, it was broken down, and yet this was not because of the failure of quinine, but because of the failure of his diagnosis. Many kinds of tropical fever which did not react to quinine were not, he was certain, either malaria or typhoid. If quinine were given by the mouth and absorbed, it was quite as effective as if given subcutaneously. The facts advanced in the paper were not, he thought, adequate to justify the sweeping conclusions drawn.

Dr. A. E. WRIGHT said he did not approve of the conclusions, neither did he approve of the methods described in the paper. The alleged increase of large mononuclears in the blood was fallacious, for no arbitrary test of size would distinguish such, as a varying amount of pressure on the films gave differences in apparent size. The percentage of lymphocytes and large mononuclears similarly did not give accurate information, as the polynuclear cells were probably destroyed. It was a point deserving consideration whether quinine would change the relative numbers of leucocytes in normal persons. It would have been desirable to have references to the number of parasites present in the supposed malarial cases to compare with the number of large mononuclear leucocytes. Malaria was probably very rare in Calcutta, and the two remaining fevers, as classified in the paper—namely, typhoid with small mononuclear leucocytes, and the inflammatory conditions with polynuclear leucocytes,—seemed to imply a hasty generalisation.

Dr. LOW thought that merely because one particular form of leucocyte was present it was not possible that any disease could be diagnosed; an excess of lymphocytes, for example,

Notes of case.—Malarial remittent, with double daily remission and highly resistant to quinine. Blood examination, October 28th; Widal for typhoid, — 1 in 20; Widal for Malta fever, — 1 in 10. Leucocyte count: polynuclears, 70·4 per cent.; lymphocytes, 13·2; large mononuclears, 16·4.

Disease, malarial remittent; C. A., male, aged 30; admitted October 17th, 1902; relieved.



occurred in other diseases than typhoid. It seemed, however, to be certain that an excess of large mononuclear leucocytes did occur with the presence of malarial parasites, and the large mononuclears could, he thought, be recognised with certainty by the microscope. The case described in which there was no response to quinine, but was diagnosed as malaria from the presence of large mononuclears, might have been allied to a form of the new fever of trypanosomiasis, peculiar to Calcutta.

Dr. B. W. GODDALL agreed that the facts advanced in the paper were not sufficient to establish the broad conclusions drawn by the author; it would remain for the observations to be confirmed by others. Serum reactions were not infallible, and possibly the different blood conditions might be equally variable.

Dr. ROGERS, in reply, pointed out that the cases of typhoid described in the paper with an excess of lymphocytes were, compared with the *Widal* test. He did not insist that every case with an excess of large mononuclear leucocytes was necessarily malarial; there might be other fevers, like trypanosomiasis, showing the same. In many cases with these present in excess, but with no parasites seen (the patients having been so largely dosed with quinine), the hypodermic administration of quinine gave no reaction. The cases were, no doubt, limited to India, but the observations were made on patients drawn from an area of thousands of square miles, and they were confirmed in one patient from a Boer camp. The large mononuclears were certainly difficult to distinguish, but the doubtful ones were probably not more than 2 or 3 per cent., as Dr. Christophers had pointed out.

LATENT EMPYEMA IN INFANTS

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HENOCH, in his 'Lectures on Children's Diseases,' refers to a form of pleurisy which is overlooked because of the *inertness of the pulmonary symptoms*. He says that "the 'latency' of the pleurisy is owing not to the nature of the disease, but to the carelessness of the physician;"—because pulmonary symptoms are ill-defined, a proper examination of the chest is omitted. He infers that this remark applies equally to purulent as to simple pleurisy. An empyema cavity may be overlooked also, because it is the second of two such cavities. But there is another class of empyema to which the following remarks refer, latent for other reasons. Pulmonary symptoms may indeed be vague; but in addition, even when a repeated careful examination of the chest has been made, no sure signs of the empyema are discoverable. There are no signs of the disease, or the evidence of intra-thoracic disease is slight, or the lesion may be observed entirely by its

